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EXAMINER
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ART UNIT	PAPER NUMBER
1648	4

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	Examiner	Group Art Unit	

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 1/3/02, 6/17/02, 11/8/02, 11/6/02, & 11/13/02.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) ~~62-81~~ 7, 9-40, 42-48, 50, & 60-81 is/are pending in the application.

Of the above claim(s) 7, 9-40, 42-48, 50, 60, 61, & 73-75 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 62-72 & 76-81 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☒ Information Disclosure Statem nt(s), PTO-1449, Paper No(s). 7

☐ Intervi w Summary, PTO-413

☒ Notice of Referenc (s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Oth r _____

Office Action Summary

This Office Action is in response to the amendment filed 6/17/02 and 11/08/02. All of the examined claims were canceled and new claims 62-81 are added and under final rejection.

Newly submitted claims 73-75 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: because they are directed to a method of use while the elected invention is a composition.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 73-75 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

This application contains claims 7, 9-40, 42-48, 50, 60, 61, and 73-75 drawn to inventions nonelected with traverse in Paper No. 9. A complete reply to this final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

The substitute specification is acknowledged. It is noted that claims were attached to the specification which are different than some of the current claims. In response to this observation, applicant states that the claims are the same. This is not understood as the copy of the claims submitted with the substitute specification are different from the (then) pending claims in that they were not multiply dependant (claims 4-6 for example) and the substitution of "SEQ ID NO. _" for Seq._" (claims 7-11 for example). In addition, when the substitute specification was filed (with paper #15), some of the claims were canceled. Therefore, it was not clear if applicant intended the substitute claims to be the claims to be examined.

The objection to claim 8 for failing to adhere to the requirements of the sequence rules is rendered moot by the cancellation of the claim.

The objection to Figure 1a, panels a-e, because they are unreadable is maintained. Applicant's attempt as correcting the unreadable figure by substituting a color photograph is not acceptable as there was no petition and statement concerning the entry of color figures submitted. Further, applicant has also submitted a sheet labeled "Fig. 1" with two panels and other

sheets of figures that do not resemble the figures originally submitted in the original application. In addition, there are new pages of test concerning figures but no instructions to enter the pages. These pages were not entered and if applicant later instructs that they be entered, they may not be entered as being considered new matter. Clarification and resolution of this is required. Applicant's response has only further muddied the waters.

The objection to the specification because the word "control" is misspelled in the table on page 38 is withdrawn in view of the correction of the spelling.

The rejection of claims 1-6, 8, and 57-59 under 35 U.S.C. § 101 because the invention as disclosed is inoperative and therefore lacks patentable utility is withdrawn in view of the cancellation of these claims. However, the rejection is applied to new claims 62-72 and 76-81 as the same rational is applicable to the new claims.

Applicant's arguments have been fully considered but are not deemed to be persuasive. Applicant argues that the specification does contain data from *in vivo* tests which show the activity of a vaccine against HIV and provide clear evidence that monkeys have

been vaccinated against HIV because the monkeys were not harmed and showed an immune response. Applicant further points to another experiment which purports to show that four out of six monkeys treated with the claimed composition controlled virus replication, as measured by plasma viremia, cytoviremia, antigenemia and the presence of proviral DNA, and normal CD4 T cell counts. Applicant asserts that these data clearly demonstrate to one of ordinary skill in the art that the vaccine based on the biologically active Tat protein is safe, immunogenic and effective in controlling viral replication and disease progression in humans and these results were published thus "confirming" that the results obtained were extremely convincing and led to phase I clinical trials.

Applicant's arguments are not persuasive for the following reasons. The assertion that monkeys have been vaccinated against HIV is not strictly correct because monkeys were vaccinated with tat, not HIV and are not naturally susceptible to HIV. The only conclusion that can be supported is that the immunized monkeys were not harmed and exhibited an immune response. As for the monkeys challenged with SHIV, this is an artificial construct that can be used to study various aspects of HIV but has not been shown by applicant to correspond to human vaccines. Applicant points to the inventor's article in *Nature Medicine*. Nowhere in that article

does it demonstrate a human vaccine. The article discloses, at best, in the abstract and at the conclusion of the discussion section that tat is a promising avenue to pursue for human vaccine development. Thus, in a peer reviewed journal, the inventor's group cannot say that the composition is an anti-HIV vaccine, only that it is worthy of more experimentation.

The rejection of claims 1-6, 8, and 57-59 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of applicant's amendment.

The rejection of claims 1-6, 8, and 57-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inducing an immune response, does not reasonably provide enablement for vaccines for treating or preventing HIV related disease is withdrawn in view of the cancellation of these claims. However, the rejection is applied to new claims 62-72 and 76-81 as the same rational is applicable to the new claims.

Applicant's arguments have been fully considered but are not deemed to be persuasive. Applicant argues that when one of ordinary skill in the art reads about an immune response, he

understands that the substance that induces such response is a candidate for a vaccine composition and asserts that it is known in the scientific community that protection is conferred by the induction of specific immune responses to pathogenic microorganisms or their products. Moreover, a specific preparation and handling of the protein is disclosed, and it can be administered after being re-suspended in a biological fluid and that administration of such preparation containing the claimed HIV-1 Tat protein according to the schedule reported to nonhuman primates confers protection against a challenge with a pathogenic SHIV, an artificial construct between SIV and HIV. To date, according to applicant, monkeys are considered the only model to evaluate the efficacy of an HIV vaccine, and demonstration of efficacy of a candidate vaccine in the monkey model constitutes a very strong rationale to proceed to testing in humans. Further, since vaccination was performed with the HIV-1 Tat, and an SHIV expressing the HIV-1 Tat was used for the challenge, Applicant asserts evidence of protection in humans as such, unlike many other HIV candidate vaccines that, in fact, are SIV vaccines and for which efficacy in humans can only be indirectly inferred. Lastly, applicant notes that the HIV-1 Tat used for monkeys' immunization has the same physical/chemical and biological characteristics as the Tat currently being produced for experimentation in humans and, therefore, the results from the

reported monkey studies allegedly fulfil the criteria of the pre-clinical testing needed for filing a request for approval for clinical trials.

Applicant's arguments are not persuasive because one of skill in the art would read about an immune response to be equivalent to, he understands that the substance that induces such a response is a candidate for a vaccine composition and asserts that it is known in the scientific community that protection is conferred by the induction of specific immune responses to pathogenic microorganisms or their products. This is not in doubt but applicant has the issue backwards: it is not does a protective vaccine have an immune response (never in doubt), but does an immune response convey protection (much more problematic). The answer is no. The examiner does have well known evidence available to the scientific community. Although nearly any protein when inoculated can cause an immune reaction, the prophylactic nature of this reaction is not guaranteed and has to be experimentally determined. Prophylaxis is defined as the prevention of disease or of a process that can lead to disease. For example, the *Illustrated Dictionary of Immunology* defines vaccine as a composition that stimulates protective antibodies and T cell immunity and induces active immunity. Paul in *Fundamental Immunology* teaches that vaccines were developed primarily as a prophylactic measure to prevent disease. This is

achieved by use of an antigenic (immunogenic) agent to actively stimulate the immunological mechanism, or the administration of chemicals or drugs to members of a community to reduce the number of carriers of a disease and to prevent others from contracting the disease. Testing protocols are designed to test the efficacy of the vaccines which include challenge trials or natural exposure to the disease agent in an endemic area. Further, he teaches that there is not always a correlation between seroconversion and protection from disease. Given the teachings in the art, it is clear that a compound that merely induces an immune response is not sufficient but must be protective to qualify as a vaccine. See at the top of page 1312: "[T]here was not always a correlation between seroconversion and protection from disease...." The only challenge studies were with an artificial virus construct in animals that do not get infected with HIV and progress to AIDS.

The ability of a vaccine to raise a protective immune response depends on the structure of the protein epitopes. Paul teaches that to determine the immunogenicity of certain regions of a protein, knowledge of the three dimensional structure of the protein is required to determine which polypeptides in a given protein would be accessible on the surface of the protein in order for the putative antigenic determinant to be bound by the antibody. In addition, Paul states that mobility of the putative antigenic

determinant within the native protein structure is also a determining factor for the binding of the antigenic determinant to an antibody. Paul points out (page 250, lines 4-8) that "Measurement of the mobility in the native protein is largely dependent on the availability of a high resolution crystal structure, so its applicability is limited to only a small subset of proteins." Riffkin et al. (*Gene*, 1995) teaches that a single amino acid change can alter the structure of the protein dramatically. Abaza et al. (*J. of Protein Chemistry*, 1992) teaches that mutations outside of the antigenic epitope exert an effect on the structure of the epitope. Because the structure of the protein determines it antigenicity and thereby its function as a vaccine, these structures cannot be predicted. In regards to the factors cited in the previous lack of utility rejection, applicant's specification does not address these factors and does not disclose that the instant invention has overcome these problems.

Applicant makes unsubstantiated assertions that monkeys are essentially model substitutes for human treatments. Applicant has presented no evidence of this. As applicant notes, success in this model only "constitutes a very *strong rationale to proceed* to testing in humans", not a reasonable expectation of success [emphasis added]. Even though the tat used in the monkey model was

human, that still does not automatically translate into an anti-HIV vaccine.

Applicant has not shown any support that the claimed invention overcomes the obstacles in this textbook evidence except to reply with unsubstantiated statements that because the claimed vaccine protects monkeys in an artificial experiment, it qualifies as a vaccine against HIV. Given the uncertainty in the vaccine art as demonstrated by the references and the lack of relevant working examples in the instant specification, the instant application is not enabled for vaccines.

The rejection of claims 1-6, 8 and 57-59 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention in regards to the "variants" of Tat is withdrawn in view of applicant's arguments.

The rejection of claims 1-6 and 8 under 35 U.S.C. § 102(a) as being anticipated by Frankel et al. (5,652,122) is withdrawn in view of the cancellation of these claims. However, the rejection

is applied to new claims 62, 65-68, 72, 76, and 79 as the same rational is applicable to the new claims.

Applicant argues that Frankel refers to "naturally-occurring amino acid sequence ... of naturally-occurring tat protein" which is allegedly qualitatively and quantitatively totally different and readily distinguishable from the definition of biologically active Tat as claimed by Applicant. It is further noted that Frankel states that it is preferred to remove the Tat cystein[sic]-rich region in order to avoid problems. Proceeding in accordance with Frankel's process would allegedly eliminate the biological activity of Tat as claimed by Applicant. In addition, according to Frankel, "It is known that the second exon is not required for activity". This, too, is argued to be different and distinguishable from the definition of biologically active Tat claimed by Applicant because the second exon of Tat and, in particular, the RGD motif therein is required for the efficient Tat uptake by dendritic cells and activated endothelial cells. Therefore, asserts applicant, Frankel's teaching is exactly the opposite of, and completely contrary to, the claimed invention.

Applicant further argues that it is important to note that none of the Examples reported by Frankel utilize a two exon Tat and that, therefore, the Tat protein utilized by Frankel and the two exon Tat protein utilized by Applicant are utterly different and

the preparation of the Tat disclosed in Frankel is traditional and would lead to an aggregated and oxidized Tat and, therefore, an inactive Tat, as indicated by the very high concentrations of the protein which are needed in order to observe any degree or level of uptake.

Applicant yet further argues that Frankel did not provide any data relative to the physical/chemical characteristics of Tat, nor to the substantially monomeric form that is required to fulfil the definition of biologically active Tat as indicated herein and the very high concentrations used by Frankel supposedly indicate that the Tat was neither substantially monomeric nor biologically active as claimed in this invention.

As applicant notes, Frankel teaches the use of Tat as a delivery system for molecules of interest in therapy which reads on a "pharmaceutical" composition. Applicant argues both that Frankel refers to a "naturally-occurring tat protein" and that it teaches a modified protein. Given that the reference discloses both natural and modified truncated protein (variants) and that it is disclosed in the reference that tat can, surprisingly, enter cells. They overcome unwanted disulfide bonding and trans-activation. Contrary to applicant's arguments that Frankel's method would produce an inactive protein, see column 15 to end of the patent and applicant's discussion on page 21, lines 15 and 16 of paper #15.

Further, applicant is arguing limitations not in the claims i.e., the requirement for a 2 exon protein and the RGD motif.

In addition, contrary to applicant's arguments, Frankel teaches in column 21, lines 1-2 that the protein should be purified to "ensure complete reduction of the cysteines". The fact that the reference does not specifically state that tat enters a particular cell at a particular concentration does not mean that it does not happen, it was not tested. These are characteristics of the protein. Further, claim 68 is a product-by-process claim and is not limited to the manipulations of the recited steps, only the structure implied by the steps. See MPEP § 2113.

Therefore, the instant claims are anticipated by Frankel et al.

The rejection of claims 1-6 and 8 under 35 U.S.C. § 102(b) as being anticipated by Aldovinni et al. (WO 87/02989) is withdrawn.

The following is a new ground of rejection necessitated by applicant's new claims:

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 62, 63, 69, 77, and 78 are rejected under 35 U.S.C. § 103(a) as obvious over Frankel et al.

The claims are directed to a tat protein or variant that is lyophilized for storage and later reconstitution. This is very conventional and so well known as a means for storing and/or transporting pharmaceutical compositions that judicial notice can be taken. It would have been obvious to one of ordinary skill in the art at the time the invention was made to freeze dry the tat preparation so as to safely store and ship it in a manner that is convenient to reconstitute and use. Therefore, the instant invention is obvious over Frankel et al.

On multiple occasions during the weeks of January 6-24, the examiner indicated allowable subject matter to applicant. Specifically, the necessary action required to place the application in condition for allowance are:

remove "vaccine" and intended use from the claims,

clarify the structure of the tat i.e., non-aggregated and non-oxidized as per the arguments,

withdraw non-elected claims, and

clarify the status of the figures.

No claims are allowed.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Papers related this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989).

The Group 1600 Fax numbers are: (703) 308-4242 and (703) 305-3014.

Unofficial communications may be faxed to: (703) 308-4426.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Stucker whose telephone number is (703) 308-4237. The examiner can normally be reached Monday to Thursday from 7:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JEFFREY STUCKER
PRIMARY EXAMINER